Study of Polymeric Film Bonding for Pharmaceutical Applications

by

Alyse Cardell

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ABSTRACT

Currently employed batch manufacturing processes for tablet-making in the pharmaceutical industry are estimated to cause the loss of as much as 25% of revenues due to batch rejection, rework and investigations. An alternate approach is being developed at the MIT-Novartis Center for Continuous Manufacturing (MITCCM) and is designed to be useful in accelerating the introduction of new drugs in the market, minimizing waste, reducing energy and raw material usage, carrying out quality checks online as opposed to post-production, and increasing the overall reliability and flexibility of the production process. To this end, we carry out a simple three step process to manufacture tablets – solution-making, casting, and compaction – to transform polymer based thin-films into tablets. By utilizing the interdiffusion model of polymer adhesion from past studies, we combine the base polymer HPMC (hydropropyl methyl cellulose) with varying amounts of a popularly used plasticizer PEG (polyethylene glycol) in order to achieve adequate bonding for thin-films. The effects of plasticizer in aiding polymer adhesion through interdiffusion are investigated by evaluating the glass transition temperatures and stress-strain characteristics. Finally, thin-film formulation, based on 9% PEG concentration, is employed for tablet-making and the effect of compaction pressure and dwell time on strength of thin-film-tablets is investigated. It is found that appropriate compaction pressure is necessary to allow bonding through interdiffusion without material failure, and larger dwell times favor strong bonding. The procedure proposed in this thesis can be applied to any polymer/plasticizer mix. Furthermore, this method illustrates the applicability of thin-films as a potential candidate for tablet making, as compared to the current powder-compaction technology.

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1. Introduction

1.1 Motivation

The tablet is currently the most common dosage form for the pharmaceutical industry. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. The current manufacturing method is split into two parts, an upstream and downstream process. The upstream process is the synthesis of the chemicals that make up the active pharmaceutical ingredient (API). This is the substance in the tablet that is pharmaceutically active. The downstream process ultimately forms the tablets after adding excipients and solvents to the APIs. An excipient is a pharmaceutically inert substance that functions as a carrier of APIs. Excipients include dilutants for size and volume control, disintegrating agents for absorption in the human body, binders for adhesion, stabilizers for shelf-life control, etc.

To manufacture these tablets, the pharmaceutical industry has been using a batch process since the late 1800's. Batch production is a manufacturing technique that moves a batch of materials process by process. Currently, tablets are created by first processes involving synthesis of the API. Then the API is ground into a powder, excipients are added, the solution is mixed together and then the powder in compacted into tablets. This process works well for large production loads, as the larger amount of API that can by synthesized at one time cuts down on the cost per tablet. However, if pharmaceutical companies want to explore new drugs on a smaller scale, the amount of overhead necessary to set up a production line is often cost prohibitive. Until now pharmaceutical companies have had high enough profit margins to offset the problems inherent in the manufacturing process of the drugs. However, the need for more efficient manufacturing processes in the pharmaceutical industry has recently been growing. Batch-based tablet manufacturing processes are costly, inefficient and have a longer production time than possible continuous manufacturing alternatives. In addition to that, it is hard to have flexibility in output with respect to market demand change or when a new drug is developed. Figure 1 shows a schematic of the two manufacturing processes side by side.

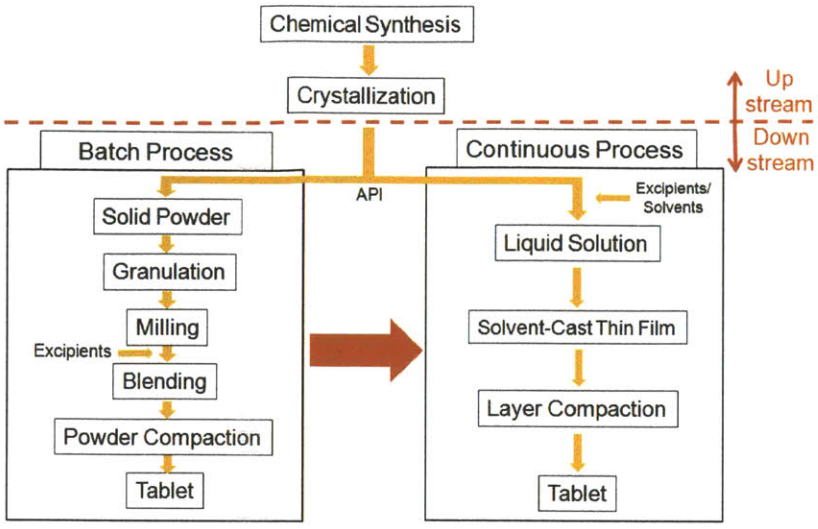


Figure 1: Schematic of the tablet manufacturing processes: (Left) conventional batch-based process, (Right) continuous process (Kim, 2010).

1.2 Continuous vs. Batch Manufacturing

Batch process manufacturing, the current industry standard, is segmented into many individual steps that are often performed at separate facilities, thereby requiring frequent disconnections in production as a batch is transported to a different facility, or loaded onto the next processing machine. In this manufacturing model, specific quantities of a drug are produced to fill an order (batch) and quality is assessed through sampling. If the quality standards are not met, the entire batch is rejected and sent back for reprocessing. It is estimated that rejected batches, rework, and investigations can use as much as 25% of pharmaceutical company revenues (Schaber, 2011).

Implementing a continuous manufacturing process would enable many changes in the pharmaceutical industry. These changes include an accelerated introduction of new drugs to market, minimal waste generation, reduction in use of energy and raw materials, continuous quality checks as opposed to post-production checks, and an overall increase in reliability and flexibility within the production process (Schaber, 2011).

1.3 Thin Films Compaction

One way to develop a continuous manufacturing process is to utilize thin films to create the tablets. In this case, the active pharmaceutical ingredient is pre-mixed with excipients to form a solution. The solution is

then cast into a thin film. Stacked layers of thin films can be compacted to form a tablet. Figure 2 shows a schematic of this tablet making process.

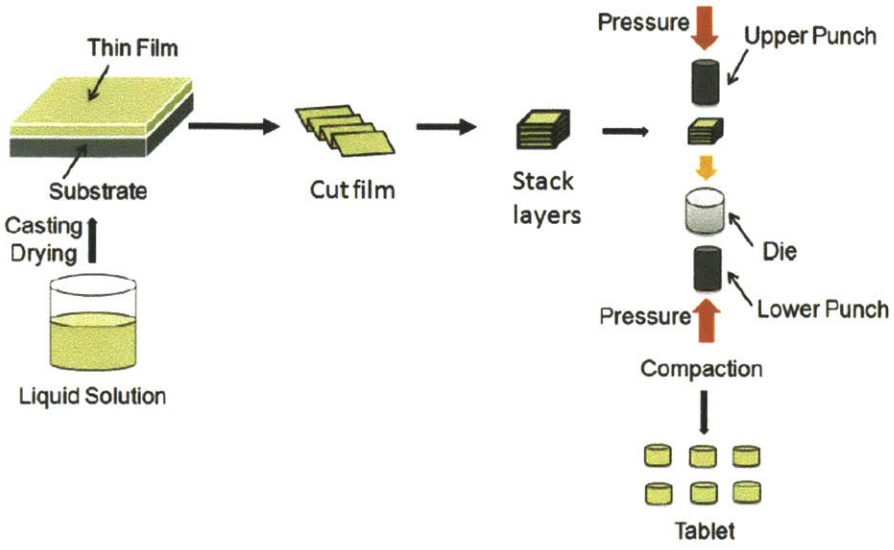


Figure 2: Schematic of continuous tablet making process using thin films

However, the use of solvent-cast thin films for the continuous tablet manufacturing process demands a fundamental understanding of layer compaction, which differs entirely from powder compaction, and will therefore need to be investigated in depth.

1.4 Thesis Objective

This thesis is focused on exploring the bonding mechanism between polymeric thin films. Understanding how these films bond is imperative in order to create the continuous manufacturing process outlined in Section 1.3. Specifically, this thesis aims to understand the role that plasticizer plays in bonding. The approach to understanding the bonding is twofold. The first step is to characterize the films and gain an idea of their mechanical properties. The second step is to investigate the effect of different amounts of pressure and dwell times on creating a successful bond.

2. Experimental Design

2.1 Model for Polymeric Film Bonding

2.1.1 Polymer Structure

The structure of polymers can be best described as long chains intertwined or entangled with each other. The individual chains are made up of a number of repeated units which are chemically bonded to each other. In this thesis, hydroxypropyl methylcellulose (HPMC) was used as the base polymer for the thin film solution. Figure 3 shows the chemical structure of HPMC.

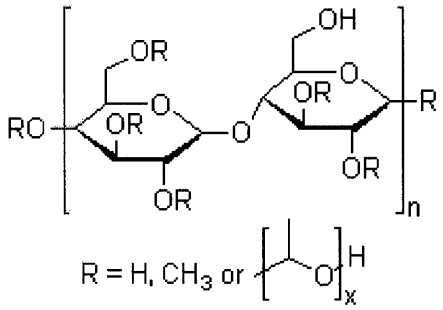


Figure 3: Chemical structure of HPMC used as polymer for thin films

The chains in polymers tend to be all coiled up and tangled together and therefore, when one begins to pull or move there is an interaction that causes the other chains to move as well. Some of the short molecules, or those with less entanglement, will slip and move more easily, while others will begin to tighten and restrict movement. Figure 4 shows a model of polymer structure.

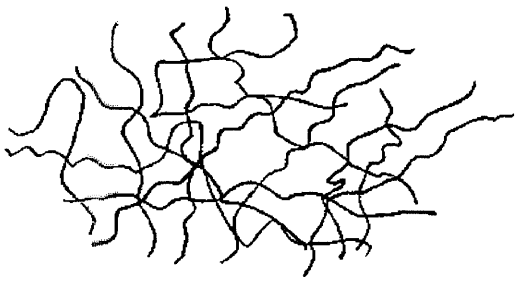


Figure 4: Diagram of multiple polymer interactions. The intertwined nature of the molecules causes a lot of interaction between the molecules.

This model for polymers will be useful in understanding the bonding process through interdiffusion and the role plasticizer plays in altering the characteristics of the polymer chains.

2.1.2 Adhesion of Polymers

Adhesion between polymers has been an active area of research. There are several theories on the mechanisms behind polymer to polymer bonding. The five main theories are as follows (Schultz, 2003) and (Allen, 2005)

1) Polymer Interdiffusion: Penetration of polymer chains into a contacting surface
2) Mechanical Interlocking: Anchoring or keying of one material into asperities, pores, or cavities of other material at the layer interface
3) Chemical Bonding: Covalent, Ionic and Hydrogen bonds
4) Physical Adsorption: Attractive forces between interface molecules because of van der Waals forces
5) Elastostatic Interactions: Electron transfer across the layer interface

Of the bonding mechanisms from the list above, chemical bonding, physical adsorption and elastostatic interactions are not applicable to macroscopic bonding at the polymer layer interface under compression, because they illustrate bonding mechanisms at the molecular level (Kim, 2010). This thesis focuses on the polymer interdiffusion model of bonding as opposed to mechanical interlocking. Typically, when mechanical interlocking is the dominant bonding mechanism, rougher surfaces bond together better than smoother surfaces. And since all the films are cast in similar conditions, the surface roughness is expected to be consistent between films. Due to the surface consistency, the polymer bonding mechanism phenomenon would not be expected to be dependent on mechanical interlocking and would instead be governed by polymer interdiffusion.

2.1.3 Polymer Interdiffusion

When two pieces of amorphous polymers are brought into contact at a temperature above the glass transition temperature, the polymeric-chains from the two sides interdiffuse. The process continues until the interface reaches the cohesive strength of the material. It is important to note that the diffusion process occurs at the temperatures above the glass transition temperature, Tg, (Brown, 1990). This can be explained based on the fact that the glass transition temperature is the temperature at which the reversible transition in amorphous materials from a hard and relatively brittle state changes into a molten or rubber-

like state. At temperatures above the Tg, the polymeric chains acquire greater mobility without any pronounced change in the material structure.

There has been a lot of research exploring polymer adhesion due to diffusion of long polymeric-chains. This research has led to a good understanding of most diffusion processes. The molecular mobility in polymers is typically described in terms of a diffusion coefficient, D. The diffusion coefficient is inversely proportional to a friction factor, c, which represents the interaction of chains with the surroundings. The addition of a plasticizer reduces the friction factor, thereby promoting polymer mobility (M.Tirrell, 1989).

Once contact is established and material is heated above Tg, the diffusion process begins and the interfacial layer of the two polymers grows quickly. The reputation model explains the movement of polymer chains. In this model, polymer movement is restricted to a tube formed by the network of surrounding chains. The polymer chains move through these tubes in a characteristic time which is proportional to the average displacement of the segments. At small times, the displacement of the chains is less than or equal to the radius of gyration of the molecule (Edwards, 1967) and (Gennes, 1971). That is, the longer the time, the more the chains have moved. Based on the background presented here, it is expected that the extent of molecular diffusion or the polymer adhesion is a function of time and shall be referred to as dwell time in this study. Figure 5 shows an image of polymer diffusion in micro layers of polyethylene and titanium dioxide over 600 seconds.

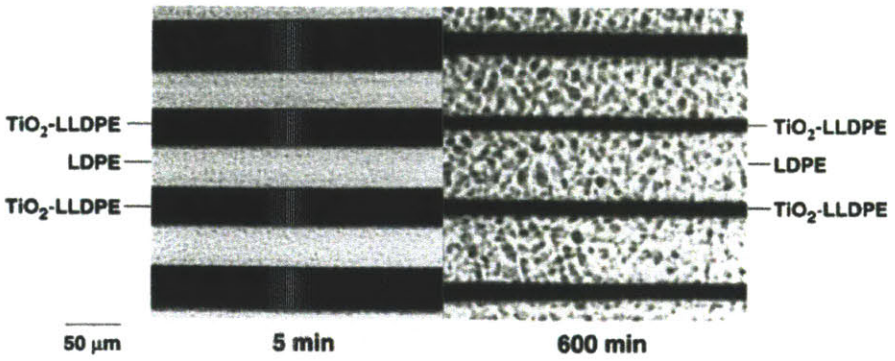


Figure 5: Optical micrographs of polymer interdiffusion of LDPE-TiO_2 –LDPE microlayers **(Nazarenko S, 1999)**.

2.1.4 Effect of Plasticizer on Mechanical Properties and Polymer Adhesion

Plasticizers are additives that provide plastics with additional flexibility and durability. Plasticizers typically have a lower molecular weight than the polymer to which they are being added, to aid dissolution. Due to their smaller size, plasticizers work by embedding themselves between the chains of polymers, spacing them apart-- which increases the free volume. Figure 6 shows a schematic of how plasticizers increase the free volume in a polymer (Galipeau, 1996).

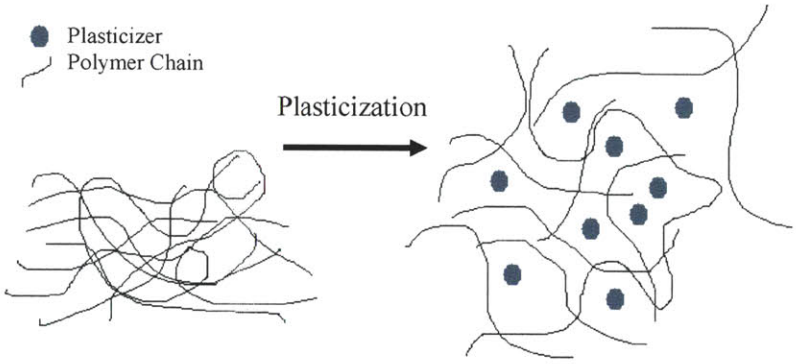


Figure 6: Schematic of plasticization, showing how the addition of a plasticizer increases the free volume in the polymer.

The mixing of the plasticizer and the polymer disrupt the secondary bonds that hold the polymer chains to one another and create more space for chain motion. The addition of plasticizers leads to a lower Tg. In this thesis, polyethylene glycol (PEG) was used as the plasticizer, and thin film formulations with varying amounts of PEG were examined. The chemical structure of PEG is shown in Figure 7.

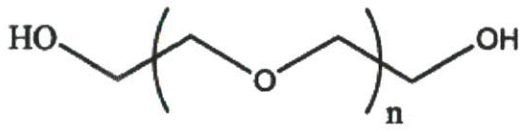


Figure 7 : Structure of polyethylene glycol (PEG) used as plasticizer in thin films.

PEG is widely used as an excipient in many pharmaceutical products. The addition of PEG has a significant effect on both the mechanical and physical properties of the films, as well as the polymer- to-polymer adhesion characteristics. Both of these effects can be understood intuitively based on the molecular description provided so far: the primary effect of weakening the interaction forces between the polymer chains due to inclusion of plasticizer allows greater stretch, because polymer motion is more independent from its surrounding entanglement, thereby affecting the mechanical and physical properties. The greater molecular mobility of the polymeric chains also enhances the interdiffusion process.

2.2 Thin Film Casting

The main focus of this thesis is to address the issue of bonding of thin films which can be used for tablet manufacturing. Since plasticizer plays a key role in the bonding process, different chemical formulations are tested by varying the plasticizer content. In this study, API was not included in the formulations and only placebo-formulations were used.

Hydroxypropyl Methylcellulose (HPMC: e3 and e15) was used as the base component in the placebo films. HPMC is a semi-synthetic, inert, visco-elastic polymer, which is popularly used as an excipient in many oral medicaments. Poly-ethylene glycol (PEG), which is compatible with HPMC, was used as the plasticizer. Distilled water and ethanol (EtOH) were used as the solvents. The placebo solution is made as follows:

1) 96 g or water is added to a beaker with a stirring apparatus
2) 15 g of MPMC e3 is added to the beaker
3) 96 g of ethyl alcohol is added
4) 15 g of HPMC e15 is added
5) 22 g of PEG is added to the solution
6) The solution is allowed to mix overnight
7) The next day the solution is allowed to rest and placed in a vacuum chamber to try to release any trapped air
8) The solution is cast

The amount of PEG was altered to test the effect of plasticizer on tablet bonding. However, preliminary experiments showed that of all the formulations, the one with 9% PEG showed the most desired properties for creating tablets, so much of the following analysis is focused on the 9% formulation.

Once the solution was created and degassed to release trapped air, it was cast on a clear polyester sheet. The casting apparatus involved a knife with adjustable height control and the samples were cast with an initial height of 0.95 mm. The polyester sheet was placed over a level stainless steel plate. Then the solution was poured onto the sheet and the knife was dragged across the solution to spread it out equally to the uniform thickness. A picture of the casting apparatus with knife and polyester is shown in Figure 8.

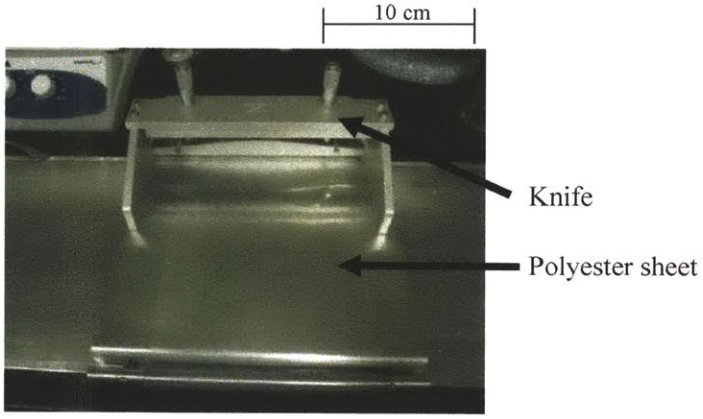


Figure 8: Casting apparatus for film with knife and polyester sheet.

The polyester sheet acts as a smooth substrate for the films to form on, but not bond to. The solvent-cast thin films were dried by natural convection in ambient conditions for about 12 hours. After drying the film, it was vacuum sealed while still on the substrate, using a VACUPACK Lite vacuum sealer. The water content was also measured in this stage. Water can act as a plasticizer and in order to observe the plasticizer effects of PEG exclusively, it was crucial to ensure that the water content was minimal. Table 1 shows the chemical formulations and water content for four different thin film formulations

Table 1: Chemical formulations and water content for thin films.

Composition					Residual Water
HPMC-e3 (g)	HPMC- e15 (g)	Water (g)	EtOH (g)	PEG (g), (% Weight)	Weight Fraction (%)
15	15	96	96	0.0, (0.1%)	2.75 %
15	15	96	96	12.0, (4.5%)	1.87 %
15	15	96	96	22.0, (9.0%)	1.67 %
15	15	96	96	44.0, (16%)	3.93 %

2.3 Cutter and Die Set

Once the films were cast, there needed to be a way to cut smaller pieces out of the large film, stack up the films, and apply pressure to bond the films. To cut out the films, a manual thin film cutter was developed. This cutter is derived from the standard die-stamping systems. The cutter cuts out the films and lets them drop into a cup. This cup is then transferred to the press, where pressure is applied to bond the films. Figure 9 shows an image of the manual thin film cutter.

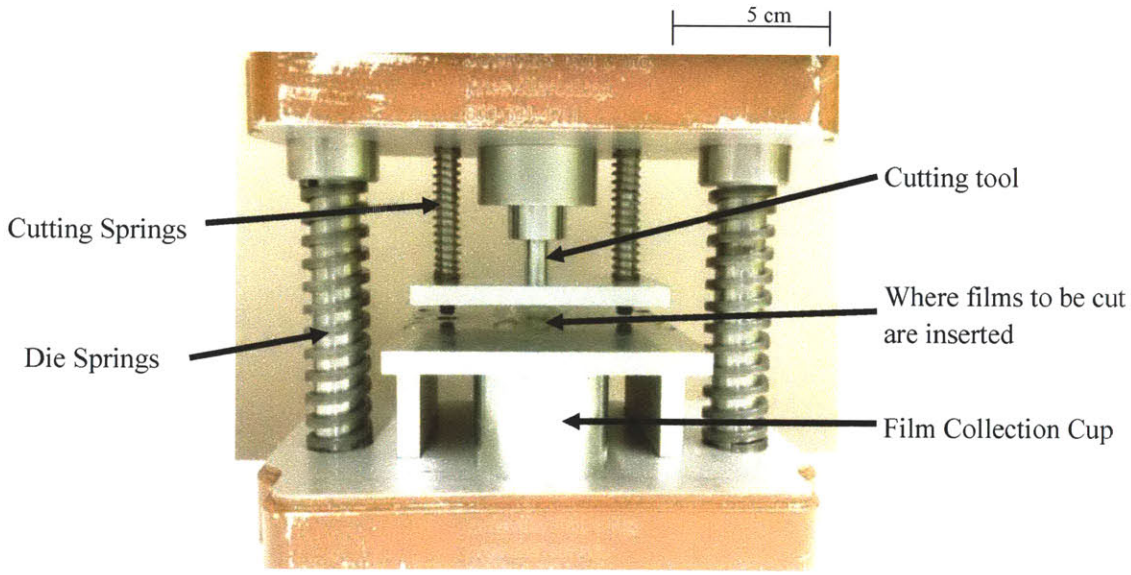


Figure 9: Picture of the manual thin films cutter used to cut out films; after the films are cut they fall into a cup that is then transferred to the die set.

The films are placed between the two metal plates shown in Figure 9. When a force is applied to the top of the cutter, the larger die springs slowly compress until the two metal plates make a flat contact. This holds the film to be cut in place. If force is still applied, the smaller cutting springs begin to compress and allow the cutting tool to punch through the thin film. The cut out film then drops into the film collection cup, at the bottom of which there are pins to align it carefully under the cutting tool, so that the films stack on top of each other nicely.

The size and shape of the films that are being cut out could be easily altered by changing the cross-sectional shape of the cutting tool and its corresponding parts. Depending on the thickness of the film and the number of layers that are cut out, the pre-compaction thickness of the tablet can be calculated.

After the films are cut out, they need to be placed in a die set to apply pressure and bond the films. The die set for compactions was designed to be compatible with a Zwick/Roell static material testing machine Z010, housed at the MIT Institute of Soldier Nanotechnologies (ISN). This machine was controlled by the TestXpert 2.0 software, which allowed different configurations to be used in the attempt to bond the films, such as variances in dwell time and pressure. A picture of the Zwick mechanical tester is shown in Figure 10.

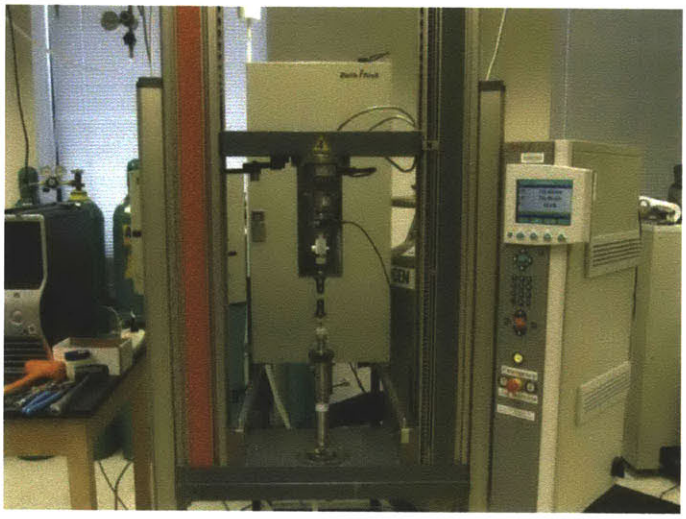


Figure 10: Picture of Zwick mechanical tester used to apply pressure to bond the films.

The compaction system has four main components: the upper head, the lower head, the compaction tool, and the collection cup. All of these pieces were made out of stainless steel. The upper and lower heads were attached to the Zwick mechanical tester using cross pins and were tightened with checknuts. The compaction tool is attached to the upper head. Figure 11 shows a solid works model for the compaction system.

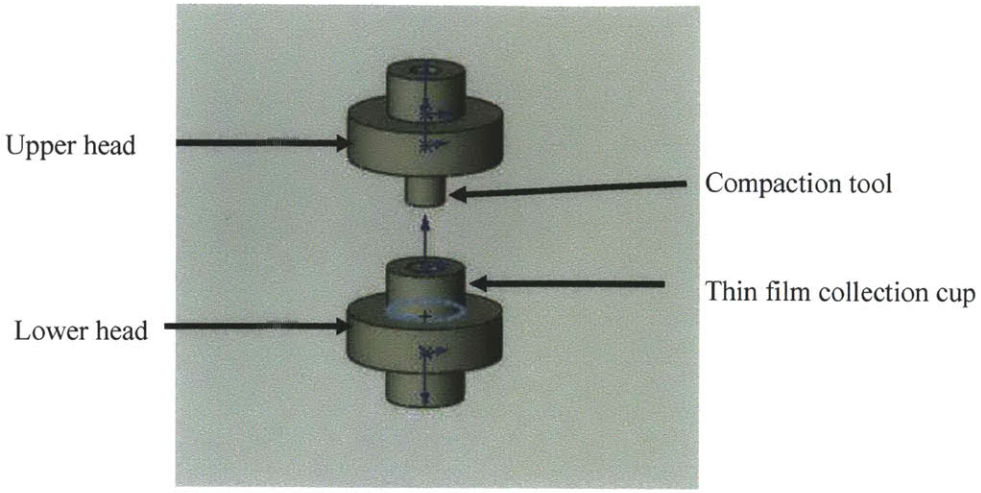


Figure 11: Solidworks model of the compaction system for thin films.

Initially, there were problems with the alignment of the compaction system. The compaction tool would scrape the side of the collection cup and lead to inaccurate readings of force. Due to this problem, controlling the pressure acting on the films was problematic. To fix this problem, a tapered compaction tool and tapered film collection cup were implemented so that they would self align as the distance between them decreased. A floating bottom for the collection cup was also implemented so that it simply sat on a plate and had a free range of motion so that it could align itself with the compaction tool. The floating arrangement allows the apparatus to compensate for any mis-alignment between the upper-head and lower-head during the mount. These changes allowed for repeatable measurements of the pressure used to bond the films. A picture of the completed die set in the Zwick mechanical tester is shown in Figure 12.

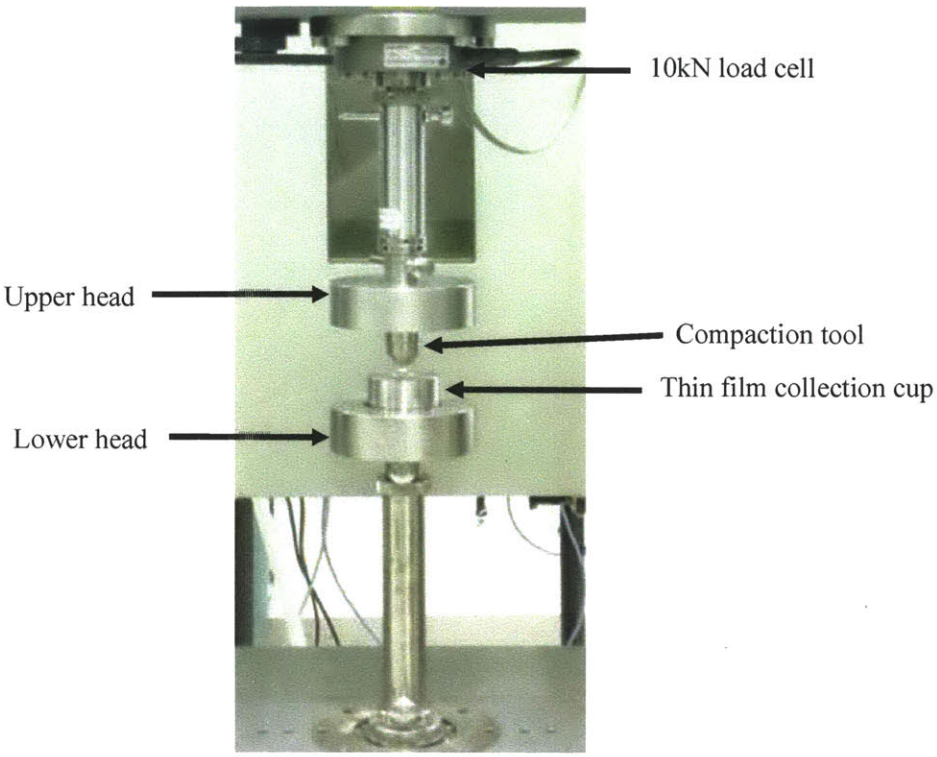


Figure 12: Picture of die set attached to the Zwick mechanical tester used to apply pressure to bond the thin films.

Based on the model for bonding discussed earlier in Section 2.1, the overall bonding of the films was studied by varying two key parameters, dwell time and compaction pressure. The die set was used to bond the films into tablets at different pressures and dwell times. A higher compaction pressure ensures better contact between the films and therefore provides larger contact area for molecules to diffuse. Also, a larger dwell time allows greater opportunities for molecular diffusion from one layer into the other. Therefore, it is expected that strong bonding between the films can be achieved at a higher compaction pressure and a larger dwell time. To form tablets, 20 film layers were stacked up and a full factorial experiment of compaction pressure and dwell time for the tableting operation was performed. Three levels for compaction pressure (10.5, 37and 73.5 MPa) and three levels for dwell time (5, 30, 60 secs.) were chosen. Table 2 summarizes the design of the experiments for this study.

Table 2: Design of experiment for compaction pressure and dwell time for tablet formation.

		Dwell Times		
		5 sec	30 sec	60 sec
Compaction Pressure	10.5 MPa	*10.5 MPa, 5 sec*	*10.5 MPa, 30 sec*	*10.5 MPa, 60 sec*
	37 MPa	*37 MPa, 5 sec*	*37 MPa, 30 sec*	*37 MPa, 60 sec*
	73.5 MPa	*73.5 MPa, 5 sec*	*73.5 MPa, 30 sec*	*73.5 MPa, 60 sec*

2.4 Tensile Testing

Tensile testing is the most fundamental type of mechanical test that can be performed on a material. Tensile tests are simple, relatively inexpensive, and fully standardized. By pulling on something, you will very quickly determine how the material will react to forces being applied. Tensile tests are used to determine the modulus of elasticity, elastic limit, elongation, proportional limit, reduction in area, tensile strength, yield point, yield strength, and other tensile properties.

Tensile testing provided us with a broad characterization of the influence of PEG on the material properties of the film. Tests were run on four levels of PEG: 0%. 4.5%, 9%,12%and 16%. The stress-strain curve relates the applied stress to the resulting strain and each material has its own unique stress-strain curve. Specimens of each film were cut to 25 mm long X 5 mm wide using a stainless steel cutter. The tensile tests were run on a TA Instruments Q800 Dynamic Mechanical Analysis (DMA) machine, which is housed in ISN. The machine parameters for the DMA are summarized in Table 3.

Table 3: Testing conditions for tensile testing on the DMA.

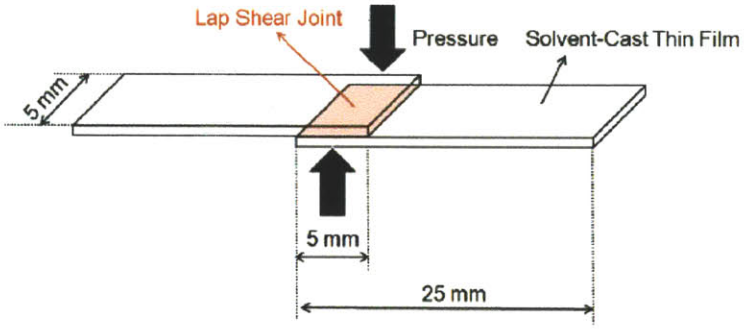
Preload	0.0010 N
Initial Strain	0.5000
Temperature (°C)	26°-28°
Displacement Rate	1500.00 µm/min
Maximum Displacement	10,000 µm

The DMA provided a better system for tensile testing of the small film samples than the Zwick mechanical tester. The DMA provides a much smaller stage to work with, which made handling and positioning the small pieces of film much easier, without compromising the sample.

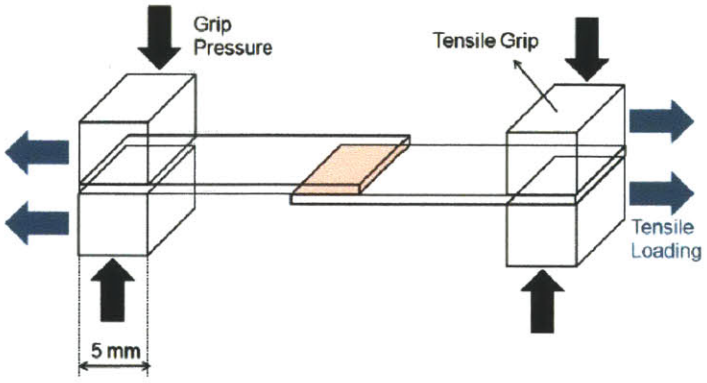
2.5 Lap Shear Testing

The next test performed to characterize the films was a lap-shear test. Lap shear tests are useful in determining the maximum force for debonding. We followed lap shear standards according to ASTM D 3163. The lap shear test has been used successfully in many prior studies of amorphous polymer bonding, such as polystyrene and polypropylene (Prud'homme, 1998).

Lap shear tests were conducted by two consecutive procedures, first the lap shear joint formation and second, the bonding strength measurement. Figure 13 shows a schematic of the two procedures involved in a lap shear test.



(a) Lap Shear Joint Formation



(b) Bonding Strength Measurement

Figure 13: Schematic of the two parts of the lap shear test, (a) formation of the lap-shear joint and (b) the measurement of the bonding force (Kim, 2010).

The lap shear joint formation was performed using the cyclic compression mode on the Zwick mechanical tester. Using this mode, both the force bonding the two films and the dwell time for which the force was applied could easily be controlled.

2.6 Tablet Strength Testing

Apart from visual inspection of pills, a Tablet Crush Tester, shown in Figure 14, is used to check for strength of thin film tablets. The tablet is placed in the loading section and the test is initiated. Initially, the tester detects the zero force configuration and the diameter of the tablet by closing the gap between the tablet and the metal bar. The test proceeds by applying pressure on the tablet until yielding occurs. The tester uses a cyclic approach and goes through a few phases of loading (crushing the pill) and unloading (pulling the metal plates apart) which gives a force reading at each cycle.

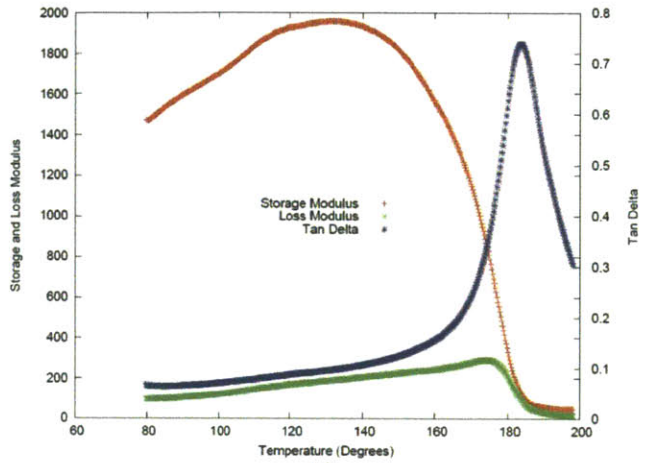
Figure 14: Dr. Schieuniger Pharmatron tablet tester.

By using the tablet tester, a qualitative view of the failure modes of the different tablets was observed. A total of 9 samples, corresponding to each operating point as shown in Table 3, were tested in the Tablet-Tester and the key observations, along with the conclusions drawn from them, are presented in Section 3.0.

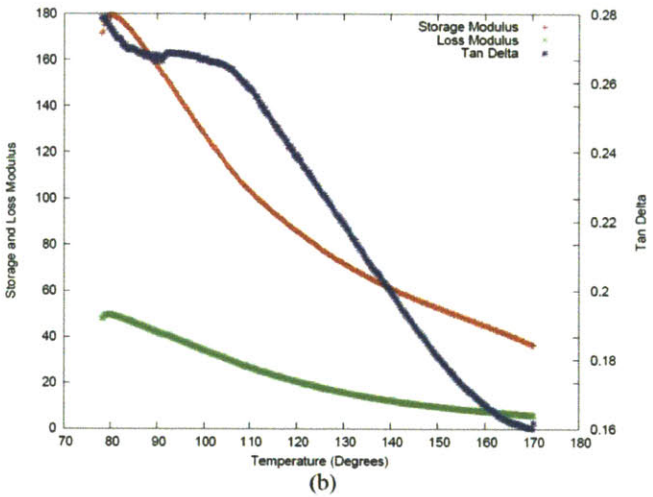
3.0 Results and Conclusions

3.1 PEG impact on Thin Film Properties

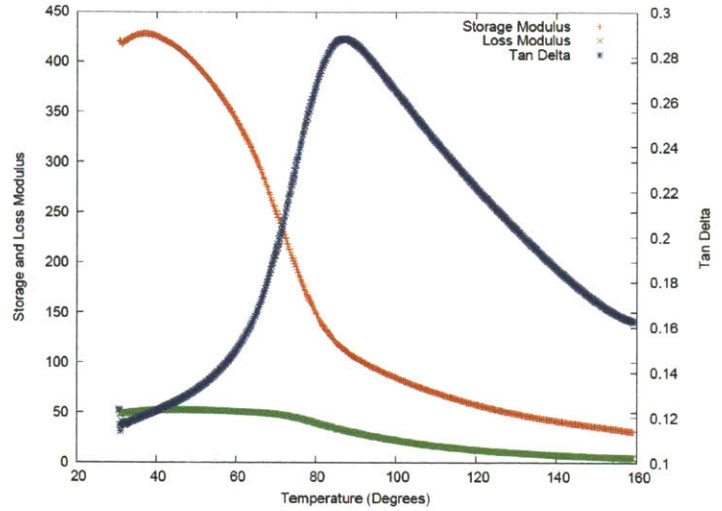
The glass transition Temperature, Tg, of the films with different PEG levels was examined using the DMA machine. Multiple samples from four different films, 0%, 4.5%, 9% and 16% PEG, were tested. The results are shown in Figure 15.



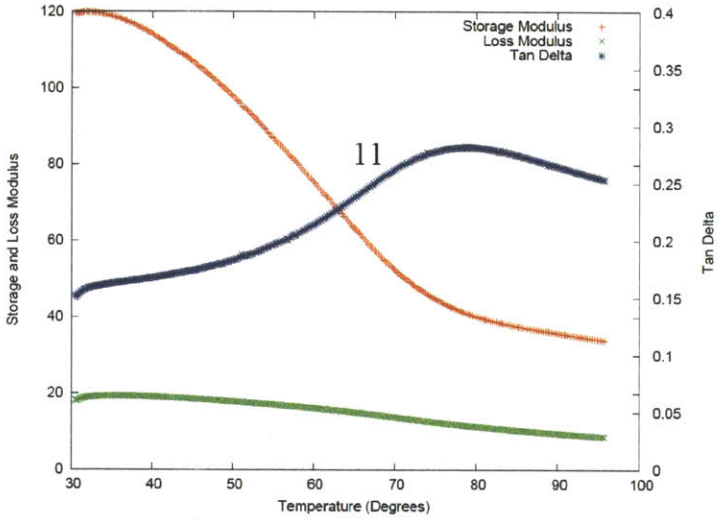
(a)



(b)



(c)



(d)

Figure 15: DMA Tg curves for (a) 0% (b) 4.5% (c) 9% and (d) 16%.

Results of the DMA testing are summarized in Figure 16.

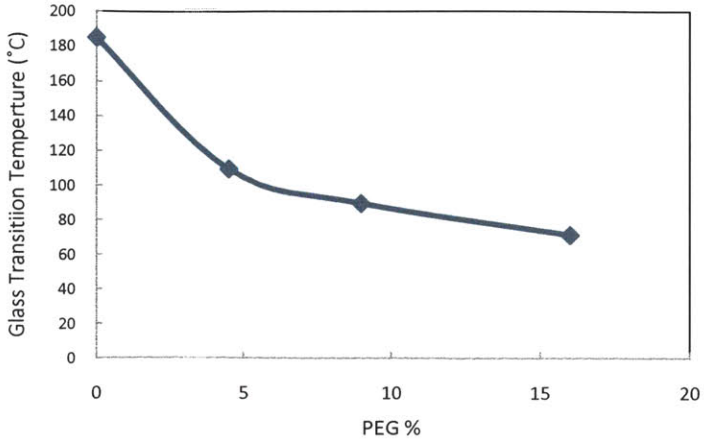


Figure 16: Graph showing relation between glass transition temperature and PEG percentage.

Figure 16 shows that increasing PEG percentage leads to lower Tg. This conforms expectations due to the diffusion bonding model, presented in Section 2.1.

The next step required to characterize the films was to perform tensile tests on four different film formulations. The resulting stress strain curves are shown in Figure 17.

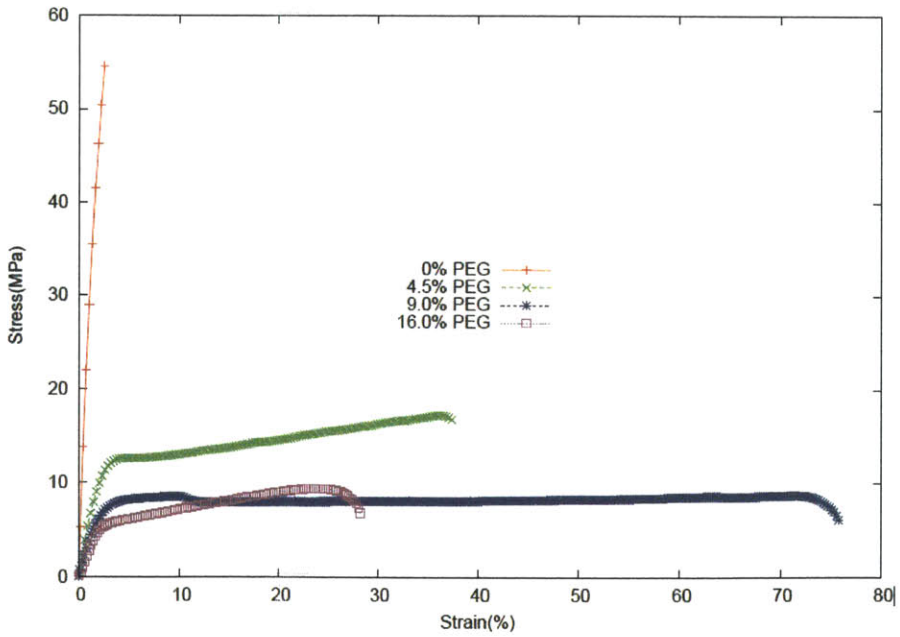


Figure 17: Stress strain curves for different amounts of PEG.

Figure 17 shows that in the film for 0% PEG, the failure occurred at small strains (0%–3.0%) while still being in the linear elastic regime. There was no definitive yield point observed in this case, which is a common characteristic of brittle materials (Jones, 2005). The addition of plasticizer resulted in a sharp reduction of yield strength, elastic modulus and stress at fracture. All PEG formulations showed an increase in fracture strain compared to 0% PEG formulation. As the concentration of PEG increases from 0%, the stress at break decreases for 4.5% and 9%, but then increases slightly for 16%.Also, the fracture strain for 16% is lower than 9% PEG. The 9% PEG stands out as it reaches a significantly higher strain than the other PEG levels. This shows that the 9% PEG is able to flow quite a bit without fracturing. This is one of the reasons the 9% PEG film was chosen for tablet analysis.

These results are congruent with the diffusion model of bonding. Incorporation of the plasticizer molecules between polymer chains disrupts polymer-polymer interactions, enabling increased polymer flexibilities, and therefore allowing the polymer matrix to sustain large deformations before fracture. The non-monotonic trend observed at 16%PEG can be attributed to the fact that with increasing amounts of plasticizer the PEG does not completely mix within the polymer in the amorphous state, and thereby the plasticization effect is reduced (Padhye, 2011). A similar trend was observed in Water-Swollen PVOH system (R. M. Hodge, 1996).

The last test that was performed was a lap shear test. Four different PEG level films were lap shear bonded at three different pressures for three different dwell times for a total of 9 variations on PEG percentage, time, and pressure. There was no bond strength in the 0% PEG film: even at the highest pressure for the longest time, the 0% PEG did not bond. Also, there was no bonding in the 16 % PEG. The higher PEG led to the film becoming too soft, and once pressure was applied, it cracked and deformed. The cracking led to a lack of strength in the bond.

Based on these experimental results, it was found that among all the formulations, the films with 9% PEG showed desired properties for tableting operation, which is why the 9% PEG formulation was used to test tablet bonding and failure, which is discussed in Section 3.2.

3.2 Tablet Bonding and Failure

Using 9% PEG, thin film formulation tablets were created following the procedure shown in Figure 2. The tablets were created by cutting and compacting the stacks of films using a set compaction pressure and a finite dwell time. Table 3 shows the compaction pressures and dwell times used to bond 9 distinct

tablet variations. As stated earlier, a higher compaction pressure ensures better contact between the films and therefore provides a larger contact area for molecules to diffuse. Also, a larger dwell time allows greater opportunities for molecular diffusion from one layer into the other. When testing the strength of the tablets, delamination, in particular, is expected to be the most frequent failure mode of layer-compacted tablets. Figure 18 shows this failure mode.

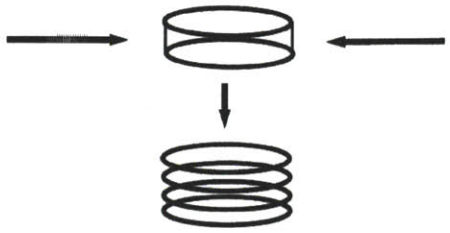
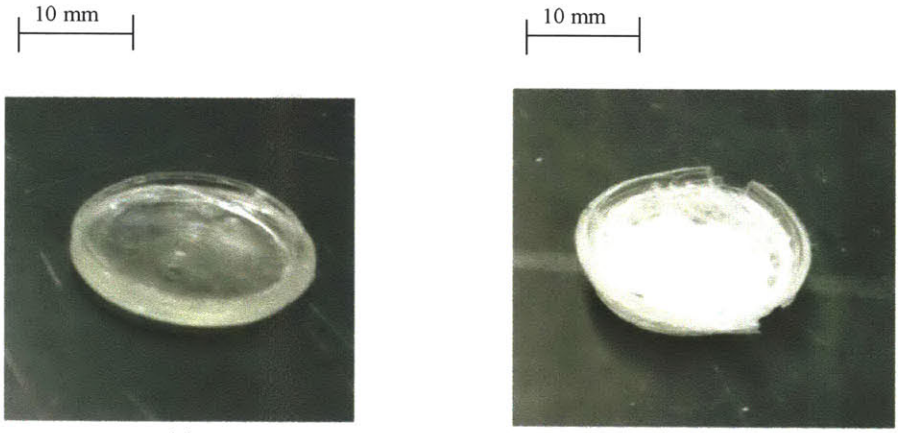


Figure 18: Failure mode for thin-film-tablets due to separation of layers.

Pictures of two of the tablets formed are shown in Figure 19, showing a well bonded tablet and a poorly bonded tablet.



(a)

Well Bonded Tablet under
37.0 MPa for 60 Sec

(b)

Fractured Tablet under
73.5MPa for 60 Sec

Figure 19: Picture of a well bonded tablet (a) and a fractured tablet (b).

Complete delamination, where all layers separate, was observed for all cases with 10.5 MPa. With 5 second dwell time, the bonding was so weak that even forces associated with manual handling led to separation of a few layers. The 60 second dwell time tablet showed slightly greater force for delamination

than the 30 second dwell time. A wide range of delamination was observed with 37 MPa. For 5 seconds, an almost complete delamination was noted. For 30 seconds, only a few delaminates occurred, whereas for 60 seconds, delamination occurred only at one location while splitting the tablet into two halves At 73.5 MPa. The observed results for all the tablets are shown in Table 4.

Table 4: Tablet crushing observed analysis for the varying time and pressure

Pressure / Time	10.5 MPa	37 MPa	73.5 MPa
5 sec	Delamination occurred while manual handling itself. Complete delamination on application of load	Almost complete delamination on application of load	Only one delamination
30 sec	Complete delamination on application of load	Partial delamination with a few layers	No delamination
60 sec	Complete delamination on application of load	Tablet split into two	No delamination

Both dwell time and compaction pressure have a noticeable effect on the bonding of thin films. Given the ranges of pressures examined, it was noticed that there exists a threshold pressure at which practically no bonding is achieved, even at high dwell times. Samples with larger dwell times often showed fewer delaminations. Thus a larger dwell time is favored for tablet strength, but it adversely affects the production rate. A pressure of 73.5 MPa lead to complete bonding, as high pressure leads to larger surface area of contact, thereby allowing greater molecular diffusion, and layers are indistinguishable from visual inspection. However, the presence of cracks and voids suggest that 73.5 MPa is close to, or beyond, the compressive strength of material and hence is not useful. Based on the data collected above, the 37 MPa with 60 secs tablet qualified best on the bonding test and still showed structural integrity (Padhye, 2011).

4.0 Conclusions and Future Work

4.1 Summary of Thesis

The overall goal of this work has been to make tablets from polymer based thin films. The overall procedure was comprised of three steps: solution making, casting, and compaction. This study considered thin film formulations based on the base polymer HPMC and the plasticizer, PEG. To find the most promising film with which to make tablets, the amount of PEG in the thin film solution was varied in an attempt to understand the role of plasticizer in bonding. It was noted that increasing plasticizer led to a decrease in Tg, decreased yield strength, and increased fracture strain. From these results, the 9% PEG film was chosen for the tableting operation.

Compaction pressure and dwell time were identified as key process parameters to obtain adhesion between the films. A two-factor three-level design of experiment was carried out for the tableting operation and the strength of tablets were tested based on a proposed delamination failure mode on a tablet tester. A compaction pressure of 37.5 MPa was found to fall within the correct operational regime. Below that, at pressures such as 10 MPa, practically no bonding was achieved due to inadequate contact between the film interfaces. At higher pressures such as 73 MPa, a high degree of bonding was achieved, but tablets showed visible failures post-compression (Padhye, 2011).

4.2 Ongoing and Future Work

This thesis attempts to explain the role of plasticizer in thin film bonding, however, more rigorous analysis must be performed to optimize the plasticizer percentage, compaction pressure, and dwell time. It has been shown that large pressures destroy thin film tablets, and small pressures do not allow the thin films to bond. Meanwhile, longer dwell times lead to better bonding than short dwell times. More analysis is required to find an optimum bonding pressure while reducing dwell time, and thus increasing the throughput of the manufacturing process.

This research would culminate in an in-house prototype for the manufacture of thin film tablets. Ideally, this process would have zero waste and would be able to be scaled up for utilization in pharmaceutical tablet manufacturing.

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